IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Boussiotis et al.	Group Art Unit: 1816
Serial No.: 08/270,152	Examiner: Gambel, P.
Filed: July 1, 1994	
For: METHODS FOR MODULATING T CELL RESPONSES BY MANIPULATING A COMMON CYTOKINE RECEPTOR GAMMA CHAIN	
Attorney Docket No.: RPI-022	

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By: _____
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PETITION UNDER 37 CFR 1.181 TO WITHDRAW FINALITY OF REJECTION

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Dear Sir:

Pursuant to 37 CFR 1.181, Applicants petition the Commissioner to withdraw the finality of the premature Final Rejection mailed on December 24, 1996 (Paper No. 15) in the above-identified patent application. The Final Rejection was improperly issued in a second Office Action because it raised a new ground of rejection not necessitated by

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amendments. Applicants did not have an opportunity to respond to the new ground of rejection nor develop clear issues before the advisability of an appeal.

It is respectfully submitted that the present petition is timely filed within two months from the action complained of pursuant to 37 C.F.R. 1.181(f) in that the Examiner's inaction up until the end of the most recent statutory period is the action complained of. Applicants requested that the Examiner withdraw the finality of the outstanding rejection in each of the responses and/or amendments filed after final. Applicants did not receive a response to these requests.

The First Office Action (mailed March 18, 1996): Overview of the Claim Rejections

Claims 48-61 were rejected in the First Office Action (Paper No. 11) under 35 U.S.C. §112, first paragraph, because according to the Examiner, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In brief, it was the Examiner's position that *in vitro* and animal model studies have not correlated well with *in vivo* clinical trial results in patients and it is not clear that reliance on the *in vitro* experimental conditions accurately reflects the relative efficacy of the claimed therapeutic strategy to stimulate T cells, (inhibit unresponsiveness). The Examiner maintained that pharmaceutical therapies are unpredictable for the following reasons: (1) the protein may be inactivated before producing an effect, (2) the protein may not reach the target area, or (3) other functional properties, known or unknown, may make the protein unsuitable for *in vivo* therapeutic use. In support of the section 112, first paragraph rejection, the Examiner also stated that there is no evidence that such an experimental model mimics the clinical situation; therefore, "the predictive value of such an *in vitro* model remains unknown." The Examiner finally argued that Applicants do not provide sufficient information or "nexus" of how to use the information gathered using T cell lines in a a clinical situation. It was the Examiner's position that administration of cytokines *in vivo* is complex.

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In further support for the section 112, first paragraph rejection, the Examiner stated that Applicants' methods are drawn to treating pathological conditions associated with tumor, pathogens, bacteria and viruses, but that these conditions are diagnosed and treated after tumor or infectious agents are already in place. The Examiner stated that Applicants have not provided sufficient evidence that indicates that there is window of opportunity to inhibit unresponsiveness and that generally, such diseases are diagnosed only after significant pathology has occurred.

In addition, it was the Examiner's opinion that "there is insufficient evidence of an appropriate agent other than γc-specific antibodies, IL-4 and IL-7; as Applicants' evidence indicates other agents do not inhibit unresponsiveness." The Examiner indicated that Applicants should limit claims to these agents.

In yet further support of the section 112, first paragraph rejection, the Examiner stated that the specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by administering an agent which modulates a signal associated with ligation of the cytokine receptor γc. The Examiner indicated that the specification does not teach how to extrapolate data obtained from *in vitro* assays associated with the molecular mechanisms of unresponsiveness in T cell links to the development of effective *in vivo* human therapeutic methods, commensurate in scope with the claimed invention.

Amendment to Claims 48-51, 56, and 59 Made After First Office Action

Claims 48-51, 56, and 59 were amended after the first Office Action as shown below.

48. (As amended) A method for modulating [unresponsiveness by a] T cell responsiveness, comprising contacting a T cell which expresses a cytokine receptor γ chain with an antibody which binds to and transduces a signal via the γ chain such that T cell responsiveness is modulated or (i) contacting a T cell which expresses a cytokine

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receptor γ chain [and has received a primary activation signal] with an agent which modulates a signal associated with ligation of the cytokine receptor γ chain such that [unresponsiveness by the] T cell responsiveness is modulated, [with the proviso that the agent does not consist of natural interleukin-2] and (ii) detecting whether signal transduction via the cytokine receptor γ chain occurs.

49. (As amended) The method of claim 48, wherein the agent stimulates a signal associated with ligation of the cytokine receptor γ chain, such that [unresponsiveness by the] T cell stimulation occurs [is inhibited].

50. (As amended) The method of claim 49, wherein the T cell has received a primary activation signal [under conditions which normally result in unresponsiveness in a T cell] in the absence of a costimulatory signal.

51. (As amended) The method of claim 50, wherein the agent acts extracellularly to stimulate a signal associated with ligation of the cytokine receptor γ chain such that [unresponsiveness by] the T cell is [inhibited] stimulated.

56. (As amended) The method of claim [51] 48, further comprising contacting the T cell with both an agent which stimulates a primary activation signal in the T cell [and an agent which stimulates a signal associated with ligation of the cytokine receptor γ chain].

59. (As amended) The method of claim 58, wherein the antigen is a pathogen or portion thereof selected from the group consisting of a virus, a bacteria, and a parasite

The Second/Final Office Action (mailed December 24, 1996): Overview of the Claim Rejections

Claims 48-61 and 97-101 were rejected in a Second/Final Office Action (Paper No. 15) under 35 U.S.C. §112, first paragraph, based on the Examiner's assertion that "there is insufficient objective evidence to support the breadth and the predictability of modulating/inhibiting responsiveness of normal or primed T cells either ex-vivo as well as in-vivo."

In support for the section 112, first paragraph rejection, the Examiner stated that "there is insufficient objective evidence to support the breadth and the predictability of modulating/inhibiting responsiveness of normal or primed T cells either ex-vivo as well as in-vivo." In particular, the Examiner stated that "the issue involved is whether or not the evidence of record, based on in-vitro studies, is generally recognized by those of ordinary skill in the art, as being ***reasonably predictive of success in the practical in-vitro and in-vivo therapeutic methods encompassed by the instant claims***." The Examiner further stated that the issue is "whether Applicants specification provides insufficient information or nexus which enables any person skilled in the art to use the full scope of the broadly claimed therapeutic methods of modulating or inhibiting unresponsiveness in T cells."

Statement of Facts: The Finality Of The Second Office Action Is Premature

No new prior art was cited against the claims in the second Office Action. There is, however, a new ground of rejection presented under 35 U.S.C., section 112, first paragraph not necessitated by Applicant's claim amendments filed in the Amendment and Response to the first Office Action (i.e., the rejection of claims 48-61).

In particular, the grounds for rejecting claims 48-61 relied on by the Examiner in the first Office Action was that "*in vitro* and animal model studies have not correlated well with *in vivo* clinical trial results in patients and it is not clear that reliance on the *in vitro* experimental conditions accurately reflects the relative efficacy of the claimed therapeutic strategy to stimulate T cells (inhibit unresponsiveness)." The Examiner further stated that "there is no evidence that such an experimental model mimics the clinical situation." Thus, in the first Office Action, the rejection was based on the Examiner's assertion that Applicants' disclosure fails to enable clinical application of the claimed methods.

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However, in the second/final Office Action, the Examiner no longer relied on an asserted failure by Applicants to enable clinical application of the claimed methods. In fact, the Examiner "agreed" at page 4, lines 6-8, of the second/final Office Action "that it is unnecessary that appellant must prove the ultimate value in humans of their asserted utility." Rather, the Examiner now stated that "there is insufficient objective evidence to support the breadth and the predictability of modulating/inhibiting responsiveness of normal or primed T cells either ex-vivo as well as in-vivo." In particular, the Examiner stated that "the issue involved is whether or not the evidence of record, based on in-vitro studies, is generally recognized by those of ordinary skill in the art, as being ***reasonably predictive of success in the practical in-vitro and in-vivo therapeutic methods encompassed by the instant claims***." The Examiner further stated that the issue is "whether Applicants specification provides insufficient information or nexus which enables any person skilled in the art to use the full scope of the broadly claimed therapeutic methods of modulating or inhibiting unresponsiveness in T cells." Applicants essentially have been deprived of an opportunity to respond to the new above-summarized grounds for rejection presented in the present Office Action prior to final.

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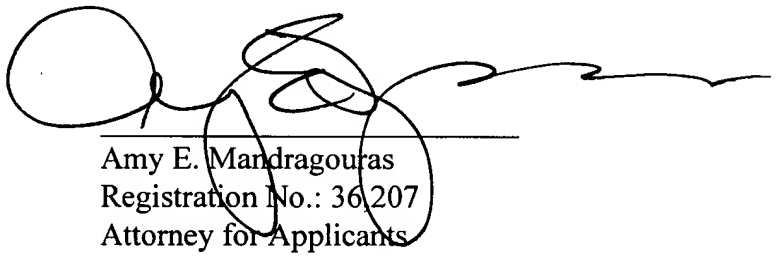
CONCLUSION

In view of the above remarks, Applicants earnestly request the Commissioner to withdraw the finality of the second Office Action to provide Applicants a full and fair opportunity to respond.

No additional fees are believed to be due in connection with this communication, however, any additional fees necessary for granting this petition can be charged to our Deposit Account No. 12-0080. A duplicate of this sheet is enclosed.

Respectfully submitted,



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